

Stochastic resonance controlled upregulation of internal noise after hearing loss as a putative correlate of tinnitus-related neuronal hyperactivity

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Abstract

Abstract

Subjective tinnitus (ST) is generally assumed to be a consequence of hearing loss (HL). In animal studies acoustic trauma can lead to behavioral signs of ST, in human studies ST patients without increased hearing thresholds were found to suffer from so called hidden HL. Additionally, ST is correlated with pathologically increased spontaneous firing rates and neuronal hyperactivity (NH) along the auditory pathway. Homeostatic plasticity (HP) has been proposed as a compensation mechanism leading to the development of NH, arguing that after HL initially decreased mean firing rates of neurons are subsequently restored by increased spontaneous rates. However all HP models fundamentally lack explanatory power since the function of keeping mean firing rate constant remains elusive as does the benefit this might have in terms of information processing. Furthermore the neural circuitry being able to perform the comparison of preferred with actual mean firing rate remains unclear. Here we propose an entirely new interpretation of ST related development of NH in terms of information theory. We suggest that stochastic resonance (SR) plays a key role in short- and long-term plasticity within the auditory system and is the ultimate cause of NH and ST. SR has been found ubiquitous in neuroscience and refers to the phenomenon that sub-threshold, unperceivable signals can be transmitted by adding noise to sensor input. We argue that after HL, SR serves to lift signals above the increased hearing threshold, hence subsequently decreasing thresholds again. The increased amount of internal noise is the correlate of the NH, which finally leads to the development of ST, due to neuronal plasticity along the auditory pathway. We demonstrate the plausibility of our hypothesis by using a computational model and provide exemplarily findings of human and animal studies that are consistent with our model.

Introduction

It is estimated that around 10 to 15 percent of the general population suffer from subjective tinnitus. This phantom percept can be very severe for affected patients and lead to insomnia, psychological disorders or even suicide (Coles, 1984; Lewis et al., 1994; Langguth et al., 2011). Tinnitus is often accompanied by a hearing loss (Heller, 2003) and recent animal studies indicate that even a relatively mild acoustic trauma may lead to a massive loss of synapses (synaptopathy) causing a so called hidden hearing loss (Liberman et al., 2015). However, an effective cure for tinnitus still does not exist, since the exact mechanisms within the auditory pathway leading to the development of tinnitus are still debated (Gerken, 1996; Eggermont, 2003; Eggermont and Roberts, 2004; Engineer et al., 2011; Knipper et al., 2011; Schaette and McAlpine, 2011; Rüttiger et al., 2013).

Some models propose a mechanism within the central auditory system called homeostatic plasticity (HP): Prolonged changes in the mean firing rates of the auditory nerve are assumed to cause HP, thereby restoring these mean firing rates and thus compensating for reduced cochlear input. This gain increase leads to increased spontaneous rates which are hypothesized to be the correlate of hyperactivity (Schaette and Kempter, 2006; Knipper et al., 2011; Schaette and McAlpine, 2011). However all HP models fundamentally lack explanatory power since it remains totally elusive why the mean firing rate of neurons should be kept constant and which benefit this might have in terms of information processing. Furthermore a concrete neural circuitry being able to perform the comparison of the preferred with the actual mean firing rate remains unclear.

Here we propose an entirely new information theory inspired interpretation of tinnitus-related development of neuronal hyperactivity. Stochastic resonance (SR) refers to the phenomenon that sub-threshold unperceivable signals can be transmitted by adding noise to the sensor input (Benzi et al., 1981; Collins et al., 1996; Levin et al., 1996; Gammaitoni et al., 1998). SR has been found ubiquitous in nature covering a wide range of systems in physical, technological and biological contexts (Wiesenfeld and Moss, 1995) and especially within the context of neuroscience (Faisal et al., 2008;

Mino et al., 2014; Douglass et al., 1993). In addition, the existence of an optimal, non-zero intensity for the added noise has been demonstrated, allowing maximization of information transmission (Wiesenfeld and Moss, 1995). In self-adaptive signal detection systems based on SR, the optimum noise level is continuously adjusted via a feed-back loop, so that the system response in terms of information throughput remains optimal, even if the properties of the input signal change. For this processing principle the term adaptive SR has been coined (Mitaim et al., 1998; Mitaim et al., 2004; Wenning et al., 2003). An objective function to quantify information content is the mutual information (MI) between the sensor input and output (Shannon, 1948). In the context of SR the MI is frequently used in theoretical approaches (Levin et al., 1996; Moss et al., 2004; Mitaim et al., 2004). The choice of the MI is natural since the fundamental purpose of any transducer is to transmit information into a subsequent information processing system. It has been shown previously that the MI as a function of noise intensity has a well-defined peak that indicates the ideal level of noise to be added to the input signal (Moss et al., 2004). However, a fundamental drawback of the MI is the impossibility of calculating it in any application of adaptive SR where the signal to be detected is unknown (Krauss et al., 2015). Furthermore, even if the underlying signal is known, the use of the MI still seems to be rather impractical within the context of neural network architectures, since calculating the MI requires evaluating probability distributions, logarithms, products and fractions. In a previous work we were able to show that this fundamental drawback can be overcome by another objective function, namely the autocorrelation (AC) of the detector response. Maximizing the output AC leads to similar or even identical estimates of optimal noise intensities for SR as the MI, yet with the decisive advantage that no knowledge of the input signal is required (Krauss et al., 2015). In addition, the evaluation of AC functions may be quite easily implemented within neural networks using delay-lines and coincidence detectors (Licklider, 1951). Remarkably, a neural architecture, resembling the aforementioned delay-lines is found in the dorsal cochlear nucleus (DCN) (Osen, 1988; Hackney et al., 1990). In addition, the DCN is the earliest processing stage in the auditory pathway

where tinnitus-related changes have been observed. Acoustic trauma leads to increased spontaneous firing rates in the DCN (Kaltenbach et al., 1998, 2000; Kaltenbach and Afrman, 2000; Brozoski et al., 2002; Kaltenbach et al., 2004), whereby the amount of this increase is correlated to the strength of the behavioral signs for tinnitus (Kaltenbach et al., 2004) and this hyperactivity is only found in regions innervated by the damaged parts of the cochlear receptor epithelium (Kaltenbach et al., 2002).

Summing up, we propose that adaptive SR based on maximizing the AC of the cochlear output is a major processing principle in the auditory system and operates both on short and long time scales to maintain maximum information detection even though the statistics of the input (sound intensities) are changing. If, due to acoustic trauma, the cochlear output is reduced then the AC calculated within the DCN decreases. Hence the internal noise generated within the DCN increases to improve information throughput again. In the case of chronic cochlear damages the internal noise is increased permanently, which is the correlate of hyperactivity often associated with subjective tinnitus.

Methods

We implemented a phenomenological model of the acoustic stimuli, the auditory nerve responses and the effects of cochlear damage to auditory nerve responses. Furthermore, we model the adaptive SR principle based on mean AC in terms of coarse-grained functional units within the DCN. We focus on input-output mappings and not on single neuron models or concrete neural network architectures. Nevertheless we emphasize that each part of the adaptive SR feedback-loop is highly biologically plausible and may be implemented in a more fine-grained model.

Distribution of sound intensities According to (Schäette et al., 2006) we assume the probability density function of the sound intensity levels I (in dB) to be Gaussian with a mean value of 40 dB and standard deviation of 25 dB. In contrast to the aforementioned study, as input to the model we do not draw independent samples from this distribution during simulation but instead used an

Ornstein-Uhlenbeck process (Uhlenbeck and Ornstein, 1930) in order to generate a correlated time series of intensity levels, yet with identical mean value and standard deviation (figure 1).

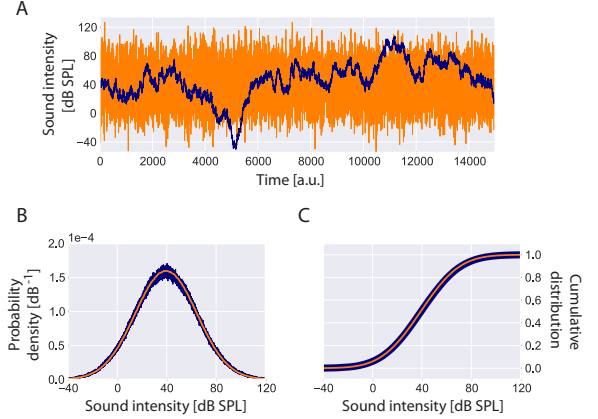


Figure 1: *Sound intensities.* Two sample time series of sound intensities are shown (A). The uncorrelated time series (orange) has been generated by drawing values from a Gaussian distribution, whereas the correlated time series (blue) is derived from an Ornstein-Uhlenbeck process. Although both time series look very different their probability density functions (B) and cumulative distributions (C) are identical.

Auditory nerve responses The firing rate $f(I)$ of the auditory nerve at a sound intensity I is modelled analogous to (Schäette et al., 2006) with a threshold I_{th} of 0 dB, spontaneous firing rate f_{sp} of 50 Hz and maximum firing rate f_{max} of 250 Hz. The response function $f(I)$ is assumed to be adapted to the distribution of sound intensities. For $I > I_{th}$, $f(I)$ is proportional to the normalized cumulative distribution function of the sound intensities hence, according to the infomax principle, $f(I)$ has maximum information on I (Laughlin, 1981). In scope of this preprint article we focus on changes to the threshold I_{th} due to cochlear damage only and do not take into account changes of the spontaneous firing rate f_{sp} or the maximum firing rate f_{max} . In figure 2 some example rate-intensity functions are shown for different thresholds.

Autocorrelation function and mean AC of auditory nerve firing rates We used the normalized autocorrelation of auditory nerve firing

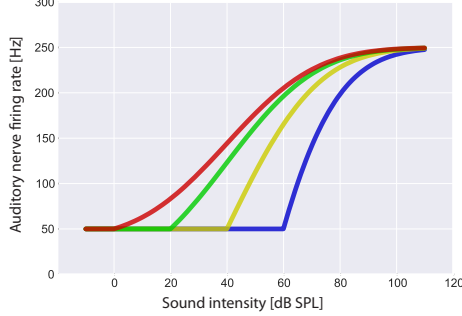


Figure 2: Rate-intensity-functions. Shown are sample rate-intensity-functions for different thresholds I_{th} at 0 dB (red), 20 dB (green), 40 dB (yellow) and 60 dB (blue). In each case the spontaneous firing rate f_{sp} is 50 Hz and the maximum firing rate f_{max} is 250 Hz.

rates $f(t)$ as a function of the time lag τ which is defined as

$$C_{ff}(\tau) = \langle (f(t) f(t+\tau)) \rangle_t \quad (1)$$

where $\langle \cdot \rangle_t$ indicates averaging over time. In order to derive a single value from this function, the mean of the autocorrelation function

$$\overline{C_{ff}} = \langle C_{ff}(\tau) \rangle_\tau \quad (2)$$

is calculated, where $\langle \cdot \rangle_\tau$ indicates averaging over all lag-times.

Adaptive stochastic resonance model Our adaptive SR model mainly consists of two functional units that build up a feedback-loop. The first unit receives input from the cochlea and calculates the AC, reflecting the information content, of the time course of auditory nerve firing rates. We refer to this unit as the information detector (ID). The second unit is controlled by the ID and injects noise to the sensory epithelium within the cochlea via efferent connections. For this part of the system we use the term noise generator (NG) (figure 3).

Implementation The model was implemented on a standard desktop PC using the programming language C/C++.

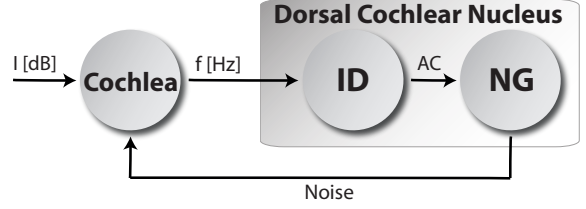


Figure 3: Adaptive SR model. The model mainly consists of two functional units that build up a feedback-loop. The information detector (ID) calculates the AC, reflecting the information content, of the time course of auditory nerve firing rates coming from the cochlea. The noise generator (NG) is controlled by the ID and injects noise to the cochlea via feedback connections. We propose that both, the ID and the NG are located within the dorsal cochlear nucleus.

Results

The aim of this study was to demonstrate how adaptive SR based on maximizing the AC may lead to permanently increased internal noise after chronic cochlear damages. Therefore we first present the effect of increased thresholds to the AC function of the time series of auditory nerve firing rates $f(t)$ and subsequently the benefit of SR to the AC.

Damage to the cochlea decreases the mean AC We evaluate the AC function of the time series of auditory nerve firing rates $f(t)$ as defined in the method section. In figure 4A autocorrelation functions for different thresholds are shown. For increased thresholds the values of the AC function systematically shift to smaller values, reflecting the decreased amount of information content perceived by the cochlea. The mean AC obtained by averaging the AC function over all evaluated lag-times decreases monotonically with increasing threshold (figure 4B).

SR improves mean AC and increases internal noise after hearing loss The beneficial effect of SR, as well as the increase of internal noise are shown in figure 5. In figure 5A a sample AC function for a threshold I_{th} of 30 dB is shown with (green) and without (red) the effect of SR. As can be clearly seen, SR is able to significantly improve the AC. The beneficial effect of SR for different

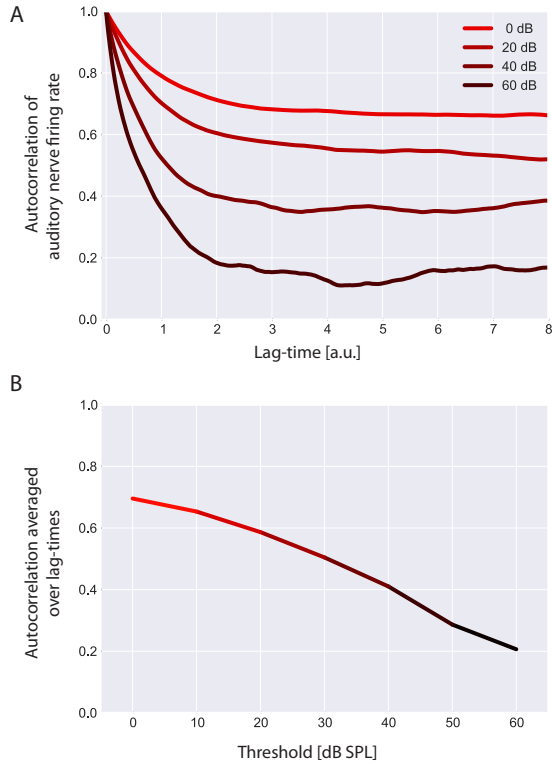


Figure 4: *Autocorrelation function of the cochlear output. Shown are the AC functions for different thresholds (A). For increased thresholds the values of the AC function systematically shift to smaller values, reflecting the decreased amount of information content perceived by the cochlea. The mean AC obtained by averaging the AC function over all evaluated lag-times decreases monotonically with increasing threshold (B).*

thresholds is summarized in figure 5B. With increasing thresholds more noise is required to improve the AC (figure 5C). This permanently increased noise is according to our hypothesis the correlate of tinnitus-related neuronal hyperactivity.

Discussion

We demonstrated how adaptive SR based on maximizing the AC of the cochlear output may cause neuronal hyperactivity in the case of chronic cochlear damages. This hyperactivity, if permanent, is thought to induce neuroplastic changes along the auditory pathway that subsequently lead to the development of subjective, central tinnitus. Further-

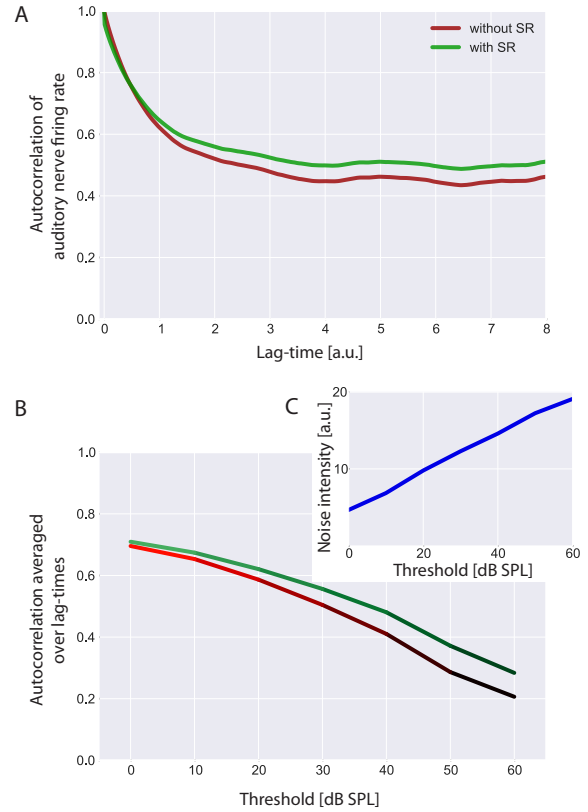


Figure 5: *Effect of stochastic resonance. In (A) a sample AC function for a threshold I_{th} of 30dB is shown with (green) and without (red) the effect of SR. As can be clearly seen, SR is able to significantly improve the AC. The beneficial effect of SR for different thresholds is summarized in (B). With increasing thresholds more noise is required to improve the AC (figure 5C).*

more, we suppose the DCN to be the site where SR is controlled. This is plausible since the neuronal architecture, i.e. delay lines and coincidence detecting neurons, required to calculate the AC are actually found within the DCN. Furthermore the DCN receives massive non-auditory input from somatosensory nuclei which may serve as some kind of internal noise, which is also required for SR.

From human studies it is known that the presentation of external noise simultaneous to pure tones is actually able to significantly improve the hearing thresholds for the pure tones via SR (Zeng et al., 2000; Ries, 2007).

Another aspect that supports our hypothesis is the so called Zwicker tone illusion. The term de-

scribes an intriguing auditory aftereffect. The typical sound generating it is a broadband noise containing a spectral gap, which is presented for several seconds. After the noise has been switched off, a faint, almost pure, tone is audible for 1 up to 6 seconds. It is decaying and has a sharp pitch in the spectral gap where no stimulus was available (Zwicker, 1964; Lummis and Guttman, 1972). Both the localization of the Zwicker tone in the brain and its origin have been long-standing open problems. In terms of our model we would expect the cause of this auditory illusion to be the SR controlled upregulated internal noise. Even though, thresholds are not increased within the channel usually processing frequencies that are within the spectral gap of the presented noise, it is plausible that cross-talk between adjacent frequency channels plays a role here. The sound intensities, or auditory nerve firing rates respectively, of neighbouring channels may serve as some kind of reference. Another finding which is perfectly consistent with our model is the fact that during the Zwicker tone sensation, auditory sensitivity for tone pulses at frequencies adjacent to the Zwicker tone are improved by up to 13 dB (Wiegand et al., 1996).

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